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Review article on a medication-induced hepatic injury causing pathological deterioration of liver function

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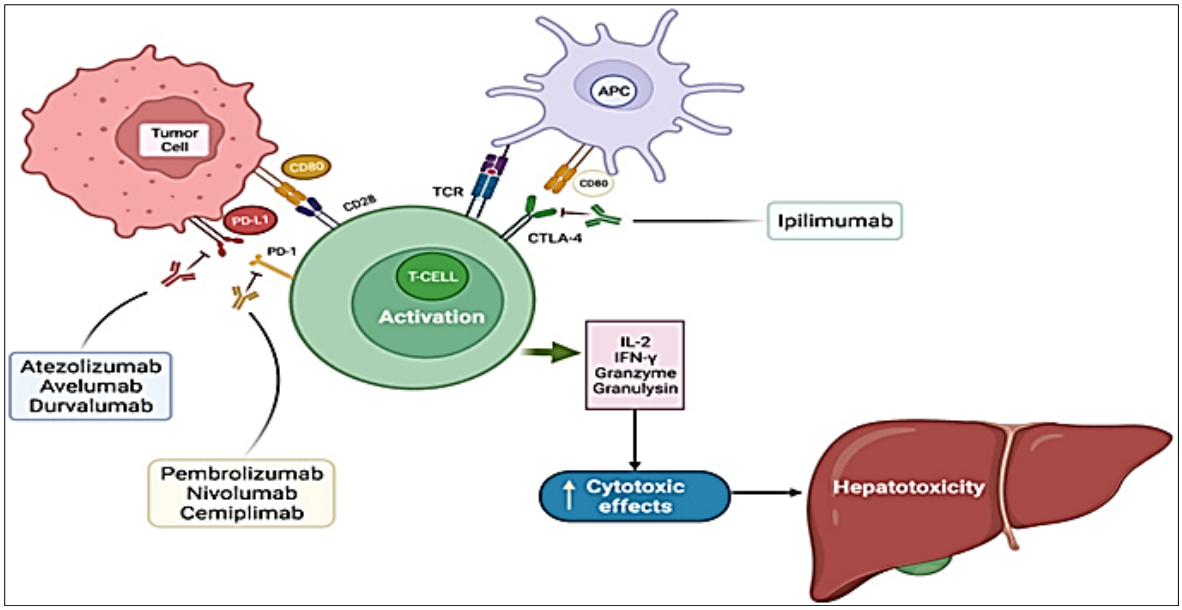
Abstract
As the body's metabolic hub, the liver plays a crucial role in sustaining internal homeostasis. It is critical for managing nutrient flow and overseeing how the body processes carbohydrates, proteins, and fats. Furthermore, medications are a common cause of liver damage. The liver's involvement in detoxifying and excreting xenobiotics renders it susceptible to their negative and toxic impacts. Liver injury caused by various poisonous chemicals or their reactive metabolites (hepatotoxicants) is known as hepatotoxicity. Some of the factors influencing an individual's vulnerability to drug-induced damage include age, gender, concurrent use of other medications, and genetic variances in metabolic pathways involved in the activation or disposal of pharmaceuticals. Despite advances, diagnosing drug-related liver injury in clinical contexts is still problematic. A broad spectrum of mechanisms is responsible for drug-related liver toxicity. Many medications have extremely reactive intermediate products generated during metabolism. Under these circumstances, whether or not hepatic damage occurs may depend on how well the drug works and how quickly the metabolite is produced.

Keywords: Liver, hepatotoxicity

1. Introduction
Through multiple functions, the liver is indispensable for sustaining and coordinating the body's homeostatic balance. It is involved in nearly every metabolic route leading to growth, illness prevention, energy provision, nutrient delivery, and reproduction [1]. Fulminant hepatic failure, or acute liver failure, is a rare but serious condition marked by rapid liver dysfunction signalled by coagulopathy, jaundice, and encephalopathy in patients without prior liver disease. In industrialized countries, it affects roughly 10 individuals per million each year, with over 2,000 cases occurring annually in the U.S. [2]. Liver disease has become a growing concern for human health in recent years. Dysregulation of liver function causes diseases such as liver fibrosis and cirrhosis, hepatitis, HCC, and fatty liver disease [3]. Disruptions to the liver's metabolizing systems can cause hepatotoxicity. Hepatotoxicity takes place through. Multiple processes are involved, including hepatocyte disintegration, apoptosis, bile duct damage, mitochondrial inhibition, and cytolytic T-cell activation. Thousands of medicines and synthetic chemicals have been linked to liver disease [4].
Medication-related liver damage, known as DILI, occurs when the liver reacts adversely to a drug. It is a rare event, with an estimated frequency of 14-19 instances per 100,000 population, contributing to less than 1% of acute liver injury (ALI). Even when a specific cause isn't identified, DILI remains the foremost cause of acute liver failure in Western regions, with a case fatality rate that can range from 10% to 50% [5]. Hepatotoxicity caused by immunotherapy can range from moderate elevations in liver aminotransferases to, in rare cases, fulminant liver failure. Clinical trial data suggest that immunotherapy-induced hepatitis is relatively uncommon, with a reported prevalence of 5.8%, though rates can vary [6].
Acetaminophen (APAP), also known as paracetamol outside the U.S. and Japan, is a widely trusted and effective drug for relieving pain and reducing fever. Though safe at normal doses, an overdose can result in serious liver damage, acute liver failure, and even death [7]. Corticosteroids or steroids have been used to treat autoimmune hepatitis (AIH) for many decades. Steroid treatments have been used since the 1970s, based on early studies that compared them to placebos. In one such study, people with a type of chronic hepatitis who

didn't have hepatitis B surface antigen (HBsAg) were given either prednisolone or a placebo. After five years, 82% of those on steroids were still alive, compared to only32% of those on placebo. Since then, many people with suspected drug-related liver damage (DILI) have been treated based on these early findings [8].

The growing incidence of herb-related liver damage is becoming a pressing issue around the world. Unfortunately, the mechanisms driving HILI are still not well defined, complicating efforts to treat and prevent it [9].



1.1 Types of DILI

Some medications cause liver damage in a consistent, dose-related fashion across all individuals—these are known as intrinsic hepatotoxins. Others, termed idiosyncratic hepatotoxins, lead to liver injury based on individual biological differences, making the reaction rare, unpredictable, and independent of dosage, route, or duration of therapy. Idiosyncratic hepatotoxicity can be characterized as metabolic or immunological. In the first scenario, DILI susceptibility depends on a specific patient's environmental setting (concomitant condition), individual's genetic susceptibility, host-related (age, gender, and ethnicity), and drug-related factors [10]. Liver damage in intrinsic DILI, such as that from acetaminophen, is clearly associated with higher doses. While idiosyncratic DILI has been considered independent of dose due to its occurrence at normal therapeutic levels, some studies now propose that dosage may still play a contributing role [11].

As immune checkpoint inhibitors (ICIs) become more widely used in cancer therapy, there's increasing recognition of the need for a third type of DILI. Indirect DILI is mechanistically different because the liver injury results from the drug's immune-modulating effects rather than its chemical properties. Although unpredictable like idiosyncratic DILI, ICI-induced liver damage is significantly more common, occurring in 5-10% of patients versus the much rarer 1 in 10,000 incidence seen with idiopathic cases [12]. Furthermore, a relatively substantial number of older, regularly given medications are well-established causes of DILI, as evidenced by a recent assessment of DILI causative agents conducted in Europe.2 Idiosyncratic DILI reactions are relatively rare (<1 in 1000 people exposed), but can have catastrophic consequences [13].

2. A Particular Medication of Exceptional Importance

2.1 | Acetaminophen

Hepatic impairment linked to acetaminophen overdose is the leading cause of liver dysfunction from pharmaceuticals, resulting in acute liver failure within the U.S. population, approximately 50% of all instances. Acetaminophen is widely used in the US and can be observed in a variety of prescriptions. Acetaminophen is a known liver toxin with a dose-dependent effect. NAPQI, a toxic compound formed during acetaminophen metabolism, is responsible for its potential to induce liver damage. (Fig. 1). [14].

Although the detailed mechanism of acetaminophen is still not well defined, it has long been classified as an NSAID, as it suppresses cyclooxygenase activity, and is frequently used as a painkiller and fever reducer. Acetaminophen has analgesic and antipyretic characteristics similar to NSAIDs, but no peripheral anti-inflammatory actions. Acetaminophen may inhibit the COX pathway. In addition, acetaminophen seems to reduce the activity of COX-1 and COX-2 enzymes without directly binding to their active sites, implying an alternative mode of action [15]. Comprehensive studies of acetaminophen-induced liver toxicity have driven remarkable progress and pinpointed novel therapeutic targets. The expanding pool of agents—especially botanical compounds—under evaluation in experimental models has also produced a number of promising antidotal candidates [16].

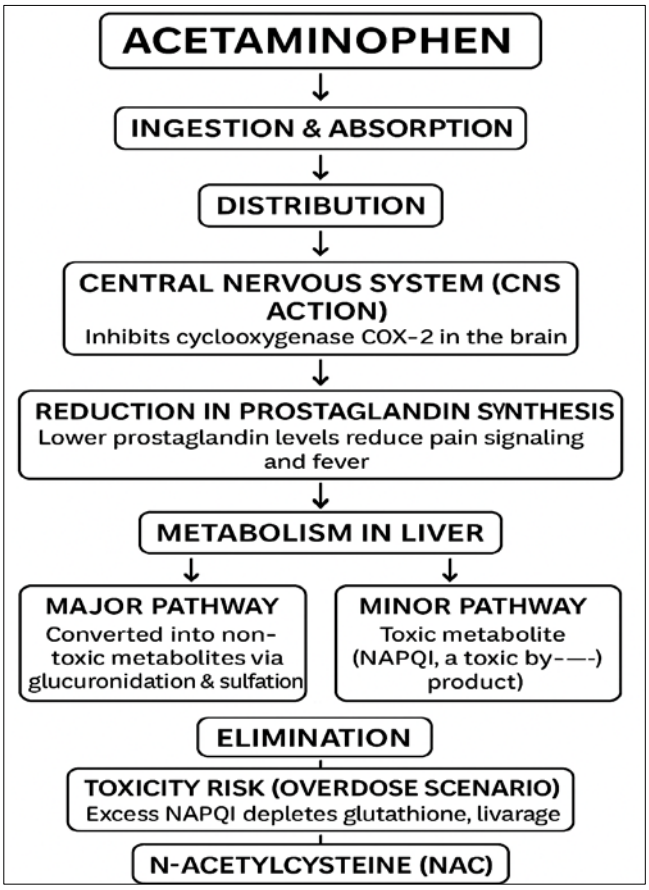


Fig 1: Potentiation of acetaminophen hepatotoxicity

2.2 Antineoplastic medicines induce liver damage

Liver damage caused by antineoplastic medications addressing liver toxicity related to chemotherapeutics, TKIs, and ICIs remains a critical concern. TKIs like erlotinib, gefitinib, lapatinib, and sorafenib have led to a breakthrough in targeted cancer therapy to supplement traditional cytotoxic treatments in cancer treatment [17]. PTK abnormalities can lead to many diseases throughout the body. Previous research indicates greater than half of the functional outputs of proto-oncogenes and oncogenes. Exhibit PTK activity, which can cause aberrant cell proliferation, regulatory disorders, and ultimately cancer [18]. When compared to standard chemotherapy, First-line administration of gefitinib in patients with EGFR-driven advanced NSCLC was associated with improved progression-free outcomes and a favourable safety profile [19]. Small-molecule TKIs and VEGF inhibitors are examples of targeted anticancer medicines that are used to treat a wide range of cancer types. These medications are intended to target specific signalling molecules or cell receptors in order to disrupt oncogenic pathways like as angiogenesis, growth signalling, and cell-cycle amplification, allowing patients to get personalized treatment depending on their cancer's mutational profile. While these medications have dramatically improved patient outcomes, they also come with a slew of negative effects, including hepatotoxicity [20].

2.3 Isoniazid and Rifampicin

First discovered 110 years ago, isoniazid has long been utilized to treat and prevent TB, with IPT being suggested for individuals with latent infections. Despite its effectiveness, INH is associated with two key toxic effects: liver injury (DILI) and damage to the peripheral nervous system [21]. INH+RIF-induced hepatotoxicity resulted in considerable elevations of serum liver enzymes [22]. Isoniazid-related liver injury is driven by a combination of biological processes, including oxidative stress, mitochondrial failure, changes in metabolic enzyme function, excess protoporphyrin IX, ER stress, bile transport dysregulation, and immune responses [23]. Rifampicin worsens liver toxicity primarily by activating cytochrome P450 enzymes, accelerating drug breakdown and boosting the formation of reactive compounds. This process heightens free radical production, resulting in oxidative stress and damage to liver cells [24].

2.4 NSAIDs (non-steroidal anti-inflammatory medicines)

Widely consumed globally, NSAIDs like ibuprofen have a low incidence of liver toxicity; however, their frequent use makes them an important factor in drug-related liver conditions. Hepatic inflammation is often driven by oxidative stress, leading to necrosis, fibrosis, lipid damage, and reduced glutathione levels [25]. Although there is a modest frequency of NSAID-induced hepatotoxicity, its widespread use creates a risk [26].

The investigation focused on exploring Nimesulide's effectiveness and capabilities an over-the-counter NSAID medicine. An evaluation of 57 hepatotoxicity cases from Spain and Latin America's DILI registry was conducted.

Several causation cases The RUCAM scale found that patients with hepatotoxicity had an average age of 59 years, with 86% being female. The average time before liver injury appeared was 40 days, with jaundice detected in 81% of

cases. Among those affected by Nimesulide, 67% experienced hepatocellular damage, 21% had mixed injury, and 12% presented with cholestasis [27].

3 Mitochondria: A Target for Hepatotoxicity and Drug-Induced Liver Injury

3.1 | Mitochondrial Functions

Mitochondria are bacterial organelles made up of two membranes that surround a compartment filled with enzymatic proteins and mitochondrial DNA. They play a crucial part in the correct function of eukaryotic cells. Energy generation, cellular metabolism regulation, and apoptosis. Healthy cells rely on mitochondria as the principal site for generating adenosine triphosphate (ATP), starting with the oxidative metabolism of nutrients like sugars, fats, and amino acids [13]. The presence of multifaceted enzyme systems—including the tricarboxylic acid cycle and electron transport chain—is responsible for this phenomenon [28].

ATP production is a fundamental and well-established function of mitochondria in cells through the process of oxidative phosphorylation. Respiratory complexes I, III, and IV constitute the electron transport chain and serve as conduits for the relay of reducing equivalents—originating from catabolic pathways such as glycolysis and the tricarboxylic acid cycle—toward dioxygen, the terminal electron acceptor assimilated via pulmonary respiration. This redox transit culminates in oxidative phosphorylation, yielding carbon dioxide and water as end-products. Though each respiratory complex can operate independently, they are also capable of forming hierarchically ordered supramolecular aggregations referred to as super complexes. These assemblies are postulated to enhance electron flux fidelity and optimize bio energetic throughput; however, their structural integration, while beneficial, is not obligatory for the sustenance of cellular viability [29]. Mitochondria, indispensable bioenergetic organelles, not only orchestrate ATP synthesis but are increasingly recognized as pivotal modulators of intracellular signaling cascades. Their central involvement in metabolic flux, coupled with their high density in hepatocellular architecture, renders them particularly susceptible to xenobiotic-induced hepatic cytotoxicity [30].

3.2 Liver Metabolic Functions and Mitochondrial Activity in Hepatocytes

Renowned for its role in sustaining energy dynamics, orchestrating nutrient metabolism, and filtering blood-borne toxins, the liver exhibits extraordinary bioenergetic capacity and ranks among the most mitochondria-enriched tissues in the body. Hepatocytes, the most common cell type in the liver, are highly specialized in diverse metabolic processes, both anabolic, such as gluconeogenesis, lipogenesis, and glutaminogenesis, and catabolic, such as glycolysis, lipolysis, and ureagenesis (Figure 2) [28].

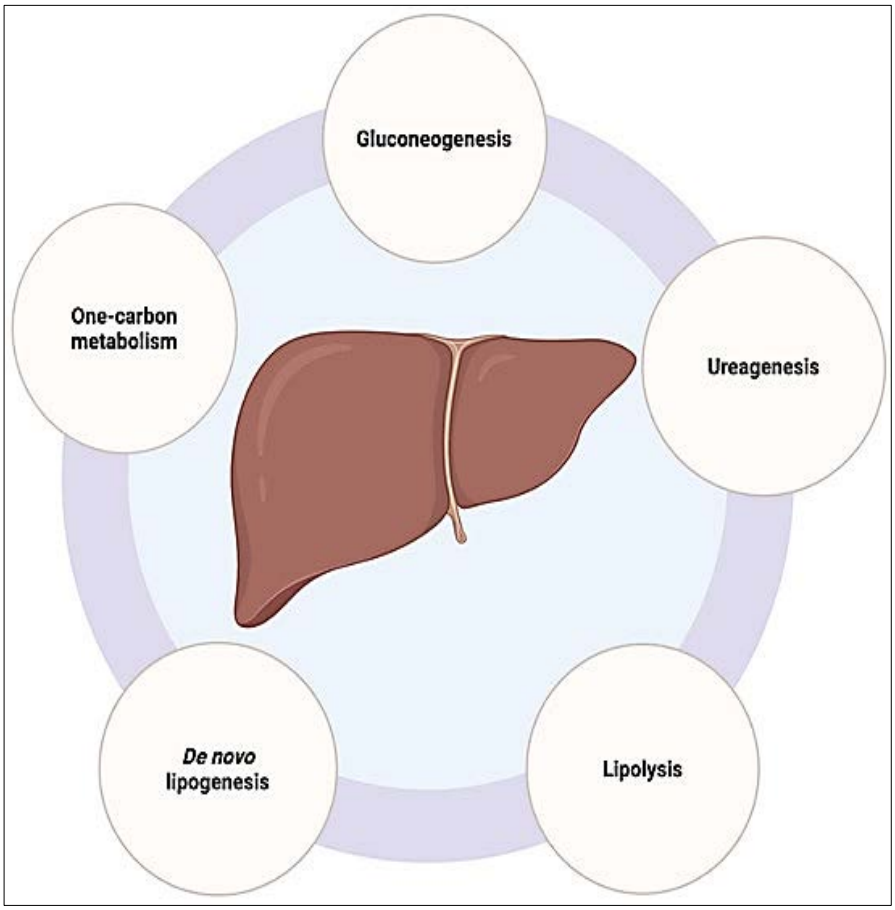


Fig 2: Schematic representation of the main hepatic metabolic functions in which mitochondria have a critical role.

3.2.1 Liver Gluconeogenesis

Hepatic gluconeogenesis, which transforms molecules such as lactic acid, glycerol, and glucose-yielding amino acids into glucose, is triggered during prolonged fasting states following glycogen depletion, with insulin and glucagon playing key modulatory roles. Gluconeogenesis accounts for

approximately half of total hepatic glucose synthesis following an overnight fast [31]. Hepatic metabolism zonation impacts hepatocyte lipid production pathways. PPHs specialize in the assimilation and metabolic breakdown of glutamine, excluding glutamate, whereas PCHs are involved in glutamine synthesis, leveraging intracellular glutamate and ammonia uptake [32]. Transaminases are essential enzymes in the gluconeogenesis and glycolysis pathways, and they can be found in many organs and tissues with significant gluconeogenesis and glycolysis activity. Transaminase activities are altered not only in the liver but also in other organs, as gluconeogenesis is modified by dietary or hormonal variables, resulting in changes in transaminase activity in the blood [33].

Substrates such as lactate, glycerol, and glucogenic amino acids (e.g., alanine and glutamine) account for the vast majority of gluconeogenesis. Lactate, a byproduct of anaerobic glycolysis, serves as the liver's principal gluconeogenic fuel, whereas glutamine leads in the renal context. However, certain studies have identified lactate as the leading substrate even in renal gluconeogenesis. The renal conversion of lactate to glucose is less than glutamine (50% vs 70% of its entire systemic gluconeogenesis) [34].

In their transcriptomic evaluation utilizing microarray profiling of OTA-exposed Hep2G hepatocellular carcinoma cells, Hundhausen *et al*. discerned significant transcriptional repression of pck2, pfkl, and pgk1 loci. The pfkl gene encodes the liver-specific isozyme of phosphofructokinase, a pivotal allosteric enzyme that mediates the rate-limiting phosphorylation of D-fructose 6-phosphate to D-fructose 1, 6-bisphosphate, thereby committing intermediates to the glycolytic cascade. Concurrently, pgk1 encodes phosphoglycerate kinase 1, a key glycolytic enzyme catalyzing the ATP-generating conversion of 1, 3-bisphosphoglycerate to 3-phosphoglycerate, integral to the substrate-level phosphorylation step of the pathway [35].

3.2.2 De Novo Lipogenesis

Hepatic de novo lipogenesis encompasses an intricate cytosolic biosynthetic pathway, whereby acetyl-CoA undergoes carboxylation to generate malonyl-CoA, serving as the principal two-carbon donor in the iterative elongation process. This mechanism proceeds via sequential cycles of Claisen-type condensations, oxidative decarboxylations, and NADPH-dependent reductions, ultimately culminating in the production of a single molecule of palmitate (C16:0). The quantification of hepatic DNL flux *in vivo* is facilitated through the administration of stable isotope-labeled precursors, allowing for precise tracking of palmitate incorporation into plasma triglyceride pools originating from hepatic lipoprotein secretion [36]. The activation of the lipogenic pathway is highly dependent on dietary circumstances. Excessive intake of carbohydrate substrates induces upregulation of hepatic de novo lipogenic flux, driven by enhanced transcriptional activation of lipogenic enzymes and coordinated metabolic signaling. Conversely, under fasting or caloric restriction, this anabolic lipid synthesis pathway is attenuated due to diminished substrate availability and suppression of associated gene expression, reflecting a metabolic shift toward energy conservation and lipid mobilization. Post-translational processes regulate lipogenic enzyme activity; however, transcription is the primary regulator. Robust induction of lipogenic enzyme gene expression is unequivocally dependent upon the synergistic activation by elevated concentrations of both insulin and glucose, which collectively serve as essential transcriptional regulators within the hepatic lipogenesis pathway [37].

Early investigations revealed that hepatic DNL did not have a substantial role in fat metabolism *in vivo*. These early findings, however, were most likely attributable to the test subjects and conditions investigated. In metabolically healthy, lean individuals subjected to fasting conditions, de novo lipogenesis (DNL) is estimated to account for under 5% of total triglyceride biosynthesis. Conversely, in postprandial states, DNL flux increases markedly—exceeding fasting rates by approximately 25% reflecting enhanced lipogenic activity driven by nutrient availability and anabolic signaling. Furthermore, hepatic lipogenesis is twice as high in the elderly as in the young [38].

3.2.3 Lipolysis

Lipolysis is defined as the catabolic mechanism that mediates the hydrolytic disassembly of TAGs into their respective building block constituents, glycerol and free fatty acids. Fat is stored in the body as adipose TAGs and used for heat, energy, and insulation. During famine, the body uses fat storage as its primary source of energy, hence preserving protein. Overall, lipids are the most significant fuel in the body, and how long a person can go without meals is primarily determined by the quantity of fat stored in adipose tissue. Lipolysis assumes a pivotal role during metabolic fasting states, wherein diminished plasma glucose concentrations necessitate alternative energy mobilization. Although this catabolic process may also proceed under basal conditions, its activation is markedly enhanced during nutrient deprivation. The hydrolytic cleavage of triacylglycerols yields glycerol, a gluconeogenic carbon substrate utilized by hepatic pathways. Concurrently, liberated free fatty acids (FFAs) circulate bound to serum albumin and undergo either mitochondrial β-oxidation within peripheral tissues or hepatic conversion into ketone bodies. The oxidative catabolism of FFAs generates ATP and NADH, both of which potentiate gluconeogenic flux. Ketogenesis in hepatocytes produces ketone bodies that serve as cerebral energy substrates, thereby alleviating reliance on depleted systemic glucose reserves [39]. Disruption in the equilibrium among lipid mobilization, uptake, synthesis, and catabolic clearance—specifically between lipolysis, lipid assimilation, lipogenesis, and lipid oxidation or export—can precipitate organelle-specific pathophysiological responses. These include endoplasmic reticulum stress, mitochondrial impairment, lysosomal destabilization, activation of c-Jun N-terminal kinase (JNK) signaling pathways, and augmented release of extracellular vesicles [40].

4 Host-Derived Predispositional Element Impacting Disease Progression.

4.1.1 | Age

The CIOMS/RUCAM causality evaluation scale now includes additional scores for patients over 55. Although older age has been hypothesized as a potential risk factor for drug-induced liver injury (DILI), large-scale registry data challenge this assumption. Specifically, the Spanish DILI Registry reported that 33% of affected individuals were aged over 65, whereas the U.S. Drug-Induced Liver Injury Network (DILIN) documented a markedly lower proportion

of 16.6% in the same age group, suggesting inconsistent age-related susceptibility across populations. An Icelandic study found that elderly people have a greater prevalence of DILI, which could be attributed to taking many medications simultaneously. Age can increase vulnerability to some medicines, leading to DILI. Drugs including isoniazid, amoxicillin-clavulanic acid, and nitrofurantoin may raise the risk of liver injury in older adults. Also included is flucloxacillin. Central nervous system pharmaceuticals, including antiepileptic and psychiatric medications, are leading causes of DILI in children. Sodium valproate with propylthiouracil may cause liver damage in younger individuals [41].

4.1.2 | Gender

Current evidence does not substantiate an elevated risk of all-cause drug-induced liver injury (DILI) among females, indicating that sex is not an independent risk determinant. Analysis of 843 documented DILI cases within the Spanish DILI Registry revealed no significant sex-based predisposition among affected individuals. They have a roughly similar gender distribution, with 48% being male. Other cohorts showed similar outcomes. Females are more likely to get liver damage from certain medicines, including minocycline and nitrofurantoin [42]. Autoimmune hepatitis (AIH) triggered by pharmacological agents—particularly minocycline and nitrofurantoin—is a recognized manifestation within the spectrum of drug-induced liver injury (DILI). In contrast, idiopathic AIH exhibits a pronounced female predominance, with women comprising approximately 80-90% of documented cases [43].

4.1.3 Alcohol

Alcohol-related liver damage can lead to severe medical, economic, and societal consequences. Alcohol-related liver pathology ranks as the fourth leading mortality determinant among urban male populations in the United States, while epidemiological trends over the past three decades reveal a substantial escalation in alcohol misuse among females. The disease begins with fatty infiltration and causes inflammation, resulting in irreparable damage. Alcohol intake causes significant changes in host defensive mechanisms, such as altered reticuloendothelial function. Immune, lymphocyte, granulocyte, and platelet function. Alcohol's impact on the reticuloendothelial system (RES) has been primarily studied because to alcoholics' susceptibility to infections. Recently, researchers have focused on the involvement of endotoxin and Kupffer cells [44]. Endotoxins cause alcohol-induced toxicity. Our hypothesis suggests that endotoxin stimulates the Kupffer cell, which is crucial for generating Parenchymal cells that experience a hypermetabolic state. This causes hypoxia in the pericentral regions of the liver lobule, resulting in toxic free radical formation and cell death upon reintroduction of oxygen [45].

4.1.4 Smoking

Cigarette smoke introduces a complex array of cytotoxic constituents that precipitate oxidative perturbations, notably via lipid peroxidation, thereby instigating hepatic stellate cell activation and fibrogenic remodeling. This pro-oxidative milieu concurrently amplifies the synthesis of inflammatory mediators—specifically interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α)—which collectively exacerbate hepatocellular injury. Empirical observations have correlated tobacco exposure with elevated hepatic fibrosis indices and intensified histopathological activity in chronic hepatitis C (CHC), as well as with the progression of cirrhotic pathology in hepatitis B virus (HBV) infection. Moreover, tobacco-induced hepatic dysregulation, in conjunction with comorbid etiologies such as transfusional hemosiderosis, ethanol-mediated cirrhosis, hemoglobinopathies like thalassemia and sideroblastic anemia, and porphyric disorders including porphyria cutanea tarda, may synergistically contribute to the pathogenesis of secondary iron overload syndromes [46].

Conclusion

The liver is a central organ in maintaining homeostasis, and liver diseases, including drug-induced liver injury (DILI), pose a growing public health challenge. DILI can be intrinsic, idiosyncratic, or indirect, with mechanisms ranging from dose-dependent toxicity to immune modulation. Medications like acetaminophen, chemotherapeutic agents, and antibiotics can cause liver damage, and the liver's complex mitochondrial functions play a crucial role in this toxicity. Factors like age, gender, alcohol consumption, and smoking can also influence susceptibility. With the increasing use of immunotherapies and other drugs, understanding the mechanisms and risks of DILI remains vital for improving prevention, diagnosis, and treatment strategies.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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